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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/857,385	07/06/2001	Joyce A. Deleo	DC-0156	4729

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EXAMINER
JAGOE, DONNA A

ART UNIT	PAPER NUMBER
1614	11

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/857,385	DELEO ET AL.	
	Examin r	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the c rresp ndenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1,5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claim 1 is pending in this application.

Response to Arguments

Applicant's arguments, see pages 3-6, filed 15 March 2003, with respect to Geyer et al. (U) under 35 U.S.C. 102(b) have been fully considered and are persuasive. The rejection of claims 1-2 has been withdrawn.

Applicant's arguments, see pages 3-6, filed 15 March 2003, with respect to Mori et al. (V) under 35 U.S.C. 102(b) have been fully considered and are persuasive. The rejection of claims 1 has been withdrawn.

Applicant's arguments filed 15 March 2003 have been fully considered but they are not persuasive with regard to the Mori et al. (V) rejection under 35 U.S.C. 103(a).

Applicant points out that Mori et al. teach doses of 3mg/kg and greater (orally) of methotrexate provides a weak analgesic effect to reduce acetic acid-induced writhing in mice. While applicant argues that methotrexate had no analgesic effect at doses up to 30 mg/kg when induced by thermal stimuli, the examiner wishes to point out that the applicant is not claiming a specific dosage range. Since Mori et al. teaches the use of methotrexate for relief of pain, it would have been obvious to treat radiculopathy, a type of pain, with methotrexate.

Claim Objection

The recitation of the treatment of individuals "in need" of the treatment of a certain condition is missing. Appropriate correction is required. A physician will

typically examine many patients with various pathologies, and only some will have a particular disease requiring a particular treatment. It has been traditional in United States practice to recite the treatment of individuals "in need" of the treatment of a certain condition so as to indicate that particular subset of patients actually in need of intervention; an alternative is to recite the treatment of an individual "suffering from" a given disease. Accordingly, the following format is preferred for claiming methods of treating: "A method for treating disease X comprising administering to an individual suffering from/in need of such treatment an effective amount of agent Y". Claims not specifying the subset of patients to be treated in this manner are generally viewed as being anticipated by any prior art method using a given agent since they read on administration to the general population and not a specified subset requiring treatment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of lower back pain with radiculopathy in an animal, it does not reasonably provide enablement for preventing lower back pain with radiculopathy in an animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: Claim 1 is drawn to a method of **preventing** and/or reducing lower back pain in an animal with an effective amount of methotrexate. The nature of the invention is extremely complex in that it encompasses the actual prevention of lower back pain with radiculopathy which has many causes (such as diabetes, meningitis, ischemic injury, herniated disk, cancer and AIDS) such that the subject treated with above compounds does not contract lower back pain with radiculopathy

Breath of the Claims: The complex of nature of the claim is greatly exacerbated by breath of the claim. The claims encompass prevention of neurological disorders in mammals, which have potentially many different causes. Lower back pain with radiculopathy has many causes such as diabetes, meningitis, ischemic injury, herniated disk, cancer and AIDS. Each of these defects may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to

actually prevent lower back pain with radiculopathy is minimal. All of the guidance provided by the specification is directed towards treatment rather than prevention of lower back pain with radiculopathy.

Working Examples: All of the working examples provided by the specification are directed toward the treatment rather than prevention of lower back pain with radiculopathy.

State of the Art: While the state of the art is relatively high with regard to **treatment of the symptoms** of lower back pain with radiculopathy, the state of the art with regard to **prevention** of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** development of lower back pain with radiculopathy

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual **prevention** of lower back pain with radiculopathy in an animal with methotrexate makes practicing the claimed invention unpredictable in terms of prevention of lower back pain with radiculopathy

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine

whether or not the combination is effective for **prevention** of lower back pain with radiculopathy since the cause of the lower back pain with radiculopathy is not clear. If unsuccessful, which is likely, given the lack of significant guidance from the specification or prior art with regard to prevention of lower back pain with radiculopathy with methotrexate, one of skill in the art would have to then either envision a modification of the pharmaceutical composition of claim 1, composition dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification of prior art regarding prevention of lower back pain with radiculopathy with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of lower back pain with radiculopathy in an animal by administration of methotrexate.

Therefore, a method of **preventing** in an animal, lower back pain with radiculopathy by administering methotrexate is not considered to be enabled by the instant specification.

N w Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Chamberlain et al. Journal of Neuro-Oncology 10/1997 (abstract).

The claim is drawn to treatment and/or reducing lower back pain with radiculopathy comprising administering methotrexate to said animal so that lower back pain is prevented or reduced.

Chamberlain et al. teach that radiculopathy, a neurologic symptom of leptomeningeal metastases (LM) from breast cancer, is treated with *inter alia* methotrexate. Two of the study patients suffered from radiculopathy (page 56, column 2, 2nd full paragraph) and all patients in the study were treated with methotrexate(page 58, column 1, 3rd full paragraph). The result is that women with LM may be palliated (reduced) with combined modality therapy (see abstract). The claim language *comprising* leaves the claim open for the inclusion of unspecified ingredients, even in major amounts. Thus, the claim reads on the combined therapy of Chamberlain et al.

2. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Leger et al. Journal of Neurology, 1992.

The claim is drawn to treatment and/or reducing lower back pain with radiculopathy comprising administering methotrexate to said animal so that lower back pain is prevented or reduced.

Leger et al. teach a Lymphoma-induced polyradiculopathy in an AIDS patient treated with *inter alia* methotrexate resulting in clinical improvement of the polyradiculopathy and complete remission on a second bone marrow biopsy (see abstract and see "Case 2", page 133, column 2).

3. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by O'Neill et al. Journal of the Neurological Sciences, 1997.

The claim is drawn to treatment and/or reducing lower back pain with radiculopathy comprising administering methotrexate to said animal so that lower back pain is prevented or reduced.

O'Neill et al. teach a patient with NIDDM and a subacute onset of painful asymmetric polyradiculopathy. Clinical improvement and resolution of nerve lumbar root enhancement occurred with treatment that includes methotrexate 2.5 mg per week and increased weekly to a maximum of 15 mg/week (page 224, column 2, 1st full paragraph).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (703) 306-5826. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3230 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Donna Jagoe
Patent Examiner
Art Unit 1614

dj
May 15, 2003

MARIANNE C. SEIDEL
SUPERVISORY PATENT EXAMINER
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